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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/588,458	08/04/2006	Susanne Matheus	MERCK-3217	5757

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EXAMINER	
KAUFMAN, CLAIRE M	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/588,458	MATHEUS ET AL.	
	Examiner	Art Unit	
	CLAIRE KAUFMAN	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *18-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-20* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/11/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 5/23/08 is acknowledged. The traversal is on the ground(s) that it would not be an undue burden to examine all groups and that Groups I and II are "*generically* directed to the formulation of the present invention and method(s) for the production thereof and/or use therefore". This is not found persuasive because the first claim is drawn to a processes of preparing a formulation, and the method of using the formulation as a medicament is a different method, requiring different searches even though both methods require a search of the formulation. Even though the search for one group might turn up some art pertinent for the other, a search is directed to references which would render the invention obvious, as well as references directed to anticipation of the invention, and therefore requires a search of relevant literature in many different areas of subject matter. Evaluation of enablement also requires search and examination which are quite distinct between the methods of Groups I-II.

The requirement is still deemed proper and is therefore made FINAL.

Information Disclosure Statement

Reference B5, CH 684 164 , was not considered because no translation was provided. References C1 and C2, Harris et al, Drug. Dev. Res, 2004, and Van Reis, Encyclopeida of Bioproc. Tech., respectively, have not been considered because the references were not submitted with the IDS.

Several WO publications (B1, B3, B4) have been indicated as duplicative on the signed IDS. They appear on the attached PTO-892 in order to have the actual documents included in the record since Applicant did not supply them and the Examiner is relying on them.

Specification

The disclosure is objected to because of the following informalities: p. 18, line 28, "thereby" is repeated.

Appropriate correction is required.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-3, 5-10 and 12-17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-13, 15-24 and 26-27 of copending Application No. 10/996,597 in view of US 6,171,586 ('586). Although the conflicting claims are not identical, they are not patentably distinct from each other because both sets of claims are drawn to a liquid formulation of EGFR antibody, including cetuximab. 10/996,597 ('597) in claim 21 recites a concentration up to 50 mg/ml, which is highly concentrated (see claims 2-3 of the instant application). Claim 19 of '597 is drawn to making the stable antibody formulation using tangential flow filtration, which is a type of ultrafilatration (see instant specification at page 7, lines 24-25). The instant claims do not recite the inclusion of a buffer, amino acid and surfactant in the formulation.

6,171,586 teach a stable aqueous pharmaceutical formulation comprising a therapeutically effective amount of an antibody not subjected to prior lyophilization, a buffer maintaining the pH in the range from about 4.5 to about 6.0, a surfactant and a polyol, along with

uses for such a formulation (see Abstract). Further disclosed is one or more other pharmaceutically acceptable carriers, excipients, or stabilizers may be included in the formulation provided such as additional buffering agents, antioxidants, and methionine (see column 23). Also disclosed is a list of buffers including citrate, acetate, histidine (an amino acid), and succinate (see column 22, lines 18-30). The polysorbates surfactants disclosed are a family of surfactants which include, polysorbates 20 (col. 22, lines 49-52). Lam et al. also discloses sodium chloride as a tonicifier that may stabilize the antibody (see Column 22-23). Stability for at least one month at room temperature is disclosed (col. 6, lines 1-2).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare the aqueous solution disclosed in '586 to further stabilize the liquid formulation claimed in the instant application. One would have been motivated to do so with a reasonable expectation of success by the teachings of '586 for increased stability for an aqueous preparation of an antibody suitable for therapeutic use.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 8, 12-17 and dependent claims 2-7 and 9-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 8 and 15 are indefinite because they recite at least one anti-EGFR antibody and/or one of its variants and/or fragments. While antibody fragments are well known in the art, it is unclear what is meant by an antibody variant.

The term "highly concentrated" in claims 1, 8, 12-17 is a relative term which renders the claims indefinite. The term "highly concentrated" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. While the specification says

on page 16, lines 20-24, that "highly concentrated" formulations according to the invention are characterized by a range of listed concentrations, it is unclear what range is intended in these claims. For example, if 10-250 mg/ml is intended, then claims 2 and 9 are not further limiting.

Claim 15 is indefinite because it is unclear how it differs from claim 8. In light of the specification, it appears that the antibody of claim is "obtainable by the process according to claim 1". Therefore, it is unclear what distinguishes the formulation of claim 15 from claim 8.

Claim 16 is unclear because it recites "as storage-stable medicament", which is confusing. If appropriate, this rejection could be obviated by replacing the phrase with --which is a storage-stable medicament--.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 8-10 and 13-17 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 03/007988 A1.

WO 03/007988 teaches a highly concentrated liquid formulation comprising the anti-EGFR antibody, Cetuximab, a humanized chimeric murine-derived monoclonal antibody, page 1, lines 15-19). The antibody concentration may be up to 25 mg/ml (p. 4, lines 15-16).

Claims 1-4, 8-11 and 15-17 are rejected under 35 U.S.C. 102(a) as being anticipated by US 2003/0138417 A1.

US 2003/0138417 teaches stable liquid formulations of antibodies, including against growth hormone (*e.g.* EGF) receptors (middle of [0039]). The antibody concentration is 100 mg/ml or greater and may include an excipient [0054]. The antibody is prepared by ultrafiltration [0040].

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Sridhar et al. (Lancet Oncol., 4(7): 397-406, July 2003) and WO 02/096457 A2.

Sridhar et al. teaches (two paragraph beginning p. 398 col. 2 with the second full paragraph) that:

> Monoclonal antibodies have been developed that target different members of the EGFR superfamily. They are highly specific with few side-effects and may be synergistic with chemotherapy and radiation....
>
> Cetuximab (IMC-C225) is a human-murine chimeric IgG monoclonal antibody that competitively binds to the extracellular domain of EGFR.... Preclinical studies show that cetuximab inhibits the proliferation of cell lines expressing EGFR and increases the cytotoxic activity of chemotherapy and radiation. Cetuximab alone and in combination with chemotherapy or radiotherapy was generally well tolerated in phase I trials.... Cetuximab in combination with chemotherapy has shown activity in head and neck and colorectal cancers with acceptable toxic effects.

Sridhar et al. also discuss other EGFR antibodies in clinical trials as cancer therapies, including EMD72000 (Table 1 and p. 400, col. 1, first full paragraph). Sridhar et al. do not discuss antibody formula concentration or the means of concentrating an antibody formulation.

WO 02/096457 teaches highly concentrated formulations of antibodies with concentration of at least 50mg/ml up to 250 mg/ml and methods of making them by ultrafiltration (p. 4, first and second full paragraphs and, *e.g.*, p. 22, first full paragraph). The

desirability of the antibody formulation is stated (p. 2, middle): "Thus, there is a demand on the market for stable, liquid, injectable antibody formulations; and, in particular, for highly concentrated stable liquid, injectable antibody formulations. There is also a need for stable aqueous solutions comprising a high concentration of antibody protein that can be used as a starting material or intermediate in process to obtain stable liquid antibody formulations of the invention." The advantage of highly concentrated formulations being suitable for pre-filled delivery devices because of the small volume needed is also discussed (p. 7, first full paragraph). Additionally taught is that the antibodies may be monoclonal, including chimeric antibodies which are humanized, antibody fragments and antibody derivatives which are PEGylated (p. 9, first full paragraph through p. 10, first full paragraph). Excipients for the formulations are disclosed (*e.g.*, middle of p. 13).

It would have been obvious to the artisan of ordinary skill at the time the invention was made to have cetuximab or other EGFR antibody in clinical trials (monoclonal and/or humanized, including EMD72000) as described by Sridhar et al. in a highly concentrated formulation because WO 02/096457 teach the demand on the market for one that can be injectable and/or can serve as a starting material or intermediate to obtain a suitable therapeutic formulation. It would have been obvious to use ultrafiltration as a means of concentrating the antibody formulation because WO 02/096457 teaches that this part of a general method for preparation of high concentrated liquid formulations.

Prior Art

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

WO 03/007988 (reference B1 cited in the IDS filed 7/11/08) is cumulative with Sidhar et al. relied on above). It is noted that US 2004/0170632 (reference A2 cited in the IDS filed 7/11/08), claims priority to PCT/EP02/06696, which published as WO 03/007988 A1, and DE 101 33 394 A1 (published Jan. 30, 2003) which teaches the same thing.

US 6,252,055 (reference A1 cited in the IDS filed 7/11/08) is cumulative with WO 02/096457 as relied upon above as teaching methods of making highly concentrated formulations of antibodies by ultrafiltration for concentrations of 100 mg/ml up to 300mg/ml (col. 2, lines 30-

37 and col. 4, lines 18-23), and also monoclonal antibodies including humanized antibodies (col. 3, lines 28-31). Likewise, concentration by means of ultrafiltration is also taught (col. 5, lines 8-19).

WO 2004/001007 (reference B4 cited in the IDS filed 7/11/08) is also cumulative with WO 02/096457 as relied up on above for teaching highly concentrated antibody formulations and methods of making them by ultrafiltration, with a desirable concentration of MAbs between 100-300mg/ml (p. 2, lines 30-31, and p. 3, line 2 and p. 16). Pharmaceutical preparations of the formulation comprising an excipient is similarly taught (*e.g.*, paragraph bridging pages 17-18). The desirability of having a highly concentrated antibody formulation is expressed as follows: (p. 2, lines20-26) "There is considerable interest in developing efficient methods of preparing highly concentration preparations of therapeutic MAbs, in order to reduce the volume of solution that contains the required dosage, and so reduce the infusion time required for administration." "There is also considerable interest in developing efficient methods for preparing highly concentrated preparations of therapeutic MAbs hat are suitable for subcutaneous administration, which have the advantage that they can be self-administered."

Alternative Names

Cetuximab is also known as MAb C225 and ERBITUX®.

EMD72000 is also known as MAb h425 and matuzumab.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Claire Kaufman, whose telephone number is (571) 272-0873. Dr. Kaufman can generally be reached Monday, Tuesday, Thursday and Friday from 9:30AM to 2:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Nickol, can be reached at (571) 272-0835.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Official papers filed by fax should be directed to (571) 273-8300. NOTE: If applicant *does* submit a paper by fax, the original signed copy should be retained by the applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Claire Kaufman, Ph.D.
/Claire Kaufman/
Patent Examiner, Art Unit 1646
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